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DATE: December 29, 1976

TO : File

FROM : Joshua Lederberg

SUBJECT: Environmental Health Sciences Research Center Application

On December 16th I met here with Dr. Robert Owens and Fred deSerres from the NIEHS with respect to the formulation of a center application.

I had spoken briefly to David Rall, the Director of NIEHS, a few months ago and it was apparent that the institute had and expected to continue to get substantial amounts of money for center development under its mandate; and furthermore that they saw a real opportunity for such a development here at Stanford.

From Dr. Owens I found that they are now funding 7 such centers: at NYU, Mt. Sinai, Harvard, Rochester, Cincinnati, Vanderbilt, and Corvallis Oregon and that they were planning to establish 2 or 3 more in the near future. They expect to work very closely with us in the preparation of a center application that would meet their requirements for relevancy. This would then have to be reviewed, presumably by a special ad hoc committee through the DRG mechanism. The focus on environmental mutagenesis that would be the natural capability of the Genetics Department is one that they were very happy to see developed. My own strategy is to plan for a relatively modest center grant - of the order of $250,000 per year for the time being - that would help sustain a significant effort within the Department of Genetics. If this is successful during the next 2 or 3 years and the stability of funding is sustained, this could then be the springboard for considering larger and more complex institutional arrangements and support therefore. Eventual budgets of the order $1 million to $2 million from NIEH sources appeared quite credible to the visitors. In addition, I have made some preliminary contacts with ERDA which has overlapping interests and concerns and believe that they are also in a position to provide substantial support for individual research programs under the aegis of this type of center. That type of cooperation does not deter but rather would gratify the NIEHS. EPA has rather more limited funds for university-type research but is another possibility. Then finally one would have to look to private sources, perhaps beginning with the Mellon Foundation for some matching funds. Among my personal connections I think it quite likely that gifts of the order of $25,000 to $50,000 per year could be obtained fairly readily if the prospective donors saw credible evidence of the long-range institutional merits of gifts of that kind.

The tentative initial research program would be divided into 3 major categories:

1. Analytical organic chemistry - this might be under Dennis Smith's direction and would exploit the capabilities that we had been developing here under NASA support for GC/MS work and the computer-based analytical capability. In particular, the metabolism of elementary carbon - which entails a range of issues from the toxic side-effects of fossil fuel utilization (note especially the hazards from coal liquefaction), and the proposed uses of activated carbon for water purification - would be a central theme of this research. The

cc: Dean Rall

relevant compounds, especially the polycyclic hydrocarbons would be prime candidates for the biological investigations of parts 2 and 3.

2. Specific mechanisms of mutagenesis. This work would be under my personal direction with the possible help of a senior research associate or eventually another junior faculty member. The main theme here is to take advantage of the technology of DNA cloning and amplification to be able to discern much more precisely the biochemical lesions that are induced by mutagens. In this respect the work could go far beyond the Ames test in providing some specific information about the category of genetic change induced by a given chemical agent. We are now working on defining efficient systems whereby a given segment of DNA in a plasmid or phage would be the focus of analysis: for example to be able to selectively detect any mutation in a small segment that results in a disruption of its genic function. Then these altered segments would be isolated and cloned and subjected to complete nucleotide sequence analysis to determine the precise nature of the lesion characteristic of a given chemical mutagen. Besides the specificity of these tests, it should be feasible to make them quantitatively more reliable and more sensitive than the existing "Ames test" procedures. This would then enable a more sophisticated correlation of mutagenic effects with carcinogenesis for a few test compounds that have been adequately investigated in animal studies and in human epidemiology. These investigations could also be correlated with (1), in a more systematic search for the components of coal tar and other particulate organic pollutants that may have even more insidious biological activity than methylcholanthrene and dibenzanthracene which are the traditional demons from the work on carcinogenesis of 50 years ago. The ready availability of these microbial genetic assays, together with methods of fractionation that are incomparably simpler and more efficient than 50 years ago prompts a reexamination of these complex natural products with the aim of finding what may be the more dangerous culprits.

3. Population genetic implications of mutagenesis: quantitative health risk studies. The management of environmental pollution has subjected the country to a series of policy storms and dilemmas that make one doubt that we are giving the highest priority of attention to the environmental additives that in fact offer the gravest health concerns. We have reached the point where we need substantially better quantitative estimations of the health risks connected with particular pollutants in order to make wise policy choices. This branch of activity may be the most important innovation of the proposed effort but it is crucial that it be initiated in very close contact with the laboratory experimental studies. As a starting point for such policy analysis, I suggested that we build more critical models of the health costs of mutagenesis than have appeared to date. Because of the complexity of the assumptions that are posited in constructing such models, it may be useful to incorporate them into functioning computer programs. Notwithstanding the dubious validity of efforts like the Club of Rome-sponsored world models, more modest and transparent efforts would have the advantage of exposing the assumptions on which different estimates of disbenefit are inferred and making it more readily possible to investigate the sensitivity of the consequences to a range of these assumptions. This is not a formidable perhaps not even an interesting task from the standpoint of computer science but the judgments are just sufficiently complex that they tend to confuse commentators who are obliged to make singular choices out of a set of 2 or 3 dozen relevant parameters that enter into such analyses. I do not want to overemphasize the modelling aspect of it since the most important input is a thorough understanding of (a) human population genetics, (b) valid types of inference concerning dose-response relationships in mutagenesis applied to populations,

and (c) the correlation of mutagenesis with carcinogenesis. (My own estimates, based on studies not as sophisticated as now proposed, have suggested that the principal health cost of most "mutagens" is not through the route of damage to the gene pool of future generations but rather via the somatic side-effect that most of these compounds exert in increasing the incidence of cancer in the present generation. However, this is not a robust inference and deserves to be analyzed much more carefully than it has been).

Even at its inception these research efforts might well benefit from some carefully thought out collaboration with faculty from other departments; and they might also embrace some additional research programs of closely relevant interest. I have been able to identify perhaps a dozen other colleagues whom I predict would have a substantial interest in relating to these developments, but I would prefer not to encumber our first initiatives with a complex administrative structure. This view is sympathetically understood by the NIEHS representatives and there is no obstacle to locating the program entirely within the framework of the Department of Genetics. However, I would certainly wish to pay special attention to possible joint-initiatives with people like Henry Epstein in Pharmacology; Dale Kaiser in Biochemistry; Ken Smith in Radiobiology; Gene Robin in Medicine; and perhaps most important of all with the new prospective appointee in Epidemiology in the Department of Family, Community and Preventive Medicine.

If there were both a very high relevance of joint interest, and an exigent need, it might be possible to extend the base of efforts to be funded from the initial grant to include some of these outside activities. However, I would hold that the only feasible way to begin is on a management model of substantial personal responsibility and a modest, empirically testable early development commensurate with that.